REMARKS

Claims 78-86 and 93-105 are pending. Claims 78, 93, and 106-108 have been amended. Support for the recitation of ablating or depleting normal spleen cells is found on page 7, lines 5-10, *inter alia*. Claims 109-113 have been added, as supported by the disclosure on page 12, lines 30-35. Claims 78-86, and 93-113 remain in the case for further consideration.

The present claims are presented to pursue a claim scope similar to the scope of claims recently allowed following Oral Proceedings in the European counterpart of the present case, EP 03 078 022.5. There are some differences in wording because the claims in Europe are second medical use claims. The corresponding second medical use claims were found by a panel of three European examiners to address the issues of disclosure under EPC Art. 76(1), which corresponds to the US to the issue of written description under Section 112. In particular, the European examiners found the disclosure of the LL2 antibody to sufficiently describe, disclose and support the genus of B cell antibodies. A written description of the use of B cells to ablate, *i.e.,* deplete, normal cells, particularly spleen cells, is clearly supported by the original description at page 7, lines 5-10 as well as the disclosure at page 12, lines 30-35, which shows that the exemplified B cell antibody targets, and therefore can be used to deplete, normal spleen cells. The main claim thus closely follows the exact language of the specification, and reconsideration and withdrawal of the rejections for lack of written description under Section 112 are respectfully requested.

While it is believed that the present claims and remarks of record fully address the rejections under Section 112 for indefiniteness and lack of written description, several points were newly raised in the Final Rejection on which applicant wishes to comment. First, the examiner notes, with respect to the statements in the Foon and Doerner declarations relating to the meaning and scope of the term immune disease, that "it is noted that expert's opinion on the ultimate legal conclusion must be supported by something more than mere conclusory statement," citing MPEP 2164.05.

The only statement in MPEP 2164.05 relating to statements of an expert is "While a later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling, applicant can offer the testimony of an expert based on the publication as evidence of the level of skill in the art at the time the application was filed. *Gould v. Quigg*, 822 F.2d 1074, 1077, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987)." In the first instance, it is noted that MPEP 2164.05 relates entirely to the issue of enablement under the first paragraph of Section 112, not definiteness under the second paragraph of Section 112, and thus the guidance of MPEP 2164.05 clearly is not appropriate in connection with the present rejection for indefiniteness. The statements offered by Foon and Doerner with respect to the term "immune disease" provide the assessment from persons

of skill in the art at the time the application was filed of the scope to be accorded the term in question with respect to an issue of definiteness under the second paragraph of Section 112. The statements therefore do not contravene MPEP 2164.05 or the corresponding case law, and are highly probative on the issue raised by the examiner. Indeed, they go the very heart of the indefiniteness rejection, which questions whether one of ordinary skill in the art at the time the application was filed would understand the metes and bounds of the term "immune disease."

The examiner urges that "the Doerner declaration and the Foon declaration cannot be used to define the term "immune disease." Drs. Doerner and Foon are not "defining" immune disease; they are attesting to the meaning that would be ascribed to this term by those of ordinary skill in the art circa 1992. The examiner also states that the Doerner and Foon declarations fail to present "necessary evidence to establish that the term is not indefinite at the time of the invention and the declarations also fails to present objective evidence applicable to the full scope of the claims."[1] However, the issue is the meaning of the scope of "immune disease" to those skilled in the art circa 1992. Therefore, the statements of persons that were skilled in the art circa 1992 does constitute objective evidence. On the other hand, in making the rejection for indefiniteness with respect to the term "immune disease" the examiner provided no evidence, merely her conclusory statement that

> the "immune disease" is not defined by the claims and the specification does not provide a standard for ascertaining the nature or parameters of the "an immune disease" that can encompass diseases with immune system being positively (e.g. autoimmune) or negatively (e.g. HIV) regulated; in turn, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the inventions or the nature or parameters by which to determine said metes and bounds.[2]

The examiner has provided no evidence of the scope of the term "immune disease" circa 1992. Applicants, by contrast, have provided declarations of experts that were active in the field at the date in question as to the meaning of this term. That evidence stands unrebutted in the record.

The next point to be addressed relates to the examiner's contention that the "there is no nexus between the art known monoclonal antibodies and the instant specification and no nexus between the known B cell antibodies and the claimed method of treating an immune disease."[3] The

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[1] Action dated 4/23/2008 at page 5.

[2] Action dated 726/2007, at page 3, emphasis in original.

[3] Action dated 4/23/2008, at page 8

information showing that monoclonal B-cell antibodies that were known circa 1992 subsequently have been demonstrated to be effective in treating autoimmune diseases was provided at the *suggestion* of Brenda Brumbeck at the Interview on 12/3/2007. Examiner Brumbeck felt that it would be important information in considering the issue of written description, since these antibodies would be other representative species falling within applicant's disclosed genus of B cell antibodies. Accordingly, this newly raised issue of "nexus" is not understood. The examiner again notes that "the genus of B-cell antibody is extremely large" and "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus," citing MPEP 2163 II.A.3a.ii.

According to MPEP 2163 II.A.3a.ii., "a 'representative number of species' means that the species which are adequately described are representative of the entire genus." Furthermore, "what constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus."

Here, one of skill in the art would recognize that the necessary common attribute for species within the genus is the ability to bind specifically to B cells, and also that applicant demonstrated possession of this invention. Although B cell antibodies may differ in their chemical structure, they are united in this common ability to bind specifically to B cells. The species of LL2/EPB2 that is named in the specification is representative of the genus of B cell antibodies that is claimed. The information requested by Ms. Brombeck of other antibodies that were known circa 1992 that later were shown to be effective in treating autoimmune diseases fits in with this determination of what constitutes a representative number of species with respect to the present invention, and demonstrates both the correctness and adequacy of applicant's disclosure that the genus of B cell antibodies share a commonalty of function that leads to efficacy in the claimed method. It is believed that this is why Ms. Brombeck felt that such information would be highly persuasive and probative. One of skill in the art quite clearly is informed by applicant's disclosure that B cell antibodies are effective in ablating normal cells, and more particularly in treating immune diseases, and therefore possession and written description are satisfied.

Two new rejections under the first paragraph of Section 112 have been raised. The first is a written description rejection that is particularly directed to claims 102 and 105, which recite that the

immune disease is a B-cell immune disease. The examiner finds this to be new matter. These claims were added in response to a suggestion in the Action dated 7/26/2007 to "amend the claims to recite the particular characteristics of the claimed "immune disease." Moreover, the specification clearly describes that the immune diseases are B-cell immune diseases. In particular, the disclosure on page 12 that LL2 targets B cells ***and*** is useful in treating immune disease provides a description that the immune disease is a B cell immune disease.

The second new rejection under the first paragraph of Section 112 is for lack of enablement. The examiner repeatedly has emphasized that the rejections in this case relate to lack of written description and not enablement. In fact, the examiner again "reminds" application of this at the top of page 11 of the current Action. However, the examiner now adds enablement to her list of rejections. This rejection appears to have been prompted by applicant's submission of articles by Steinfeld and Doerner showing efficacy of LL2 in treating SLE and primary Sjögren's syndrome, and notations of the use by other companies of other B cell antibodies to treat rheumatoid arthritis. The examiner again cites a need for "nexus," by urging that "applicant has not provided any nexus between the prior art diseases systemic lupus erythematosus, primary Sjögren's syndrome and rheumatoid arthritis and the instant specification." The "nexus" is that all of these diseases are known to be (auto)immune diseases, which is clearly a nexus to the instant specification.

The examiner further notes comments by applicants that only those antibodies that bind antigens well expressed on normal B cells would be effective in treating immune diseases… yet the instant claims recite any B-cell antibody or fragment thereof without considering the level of antigens that is expressed on normal B cells. Thus, one of skill in the art would not be able to make and use the claimed invention of a method of treating immune diseases using any B-cell antibodies."[4] The comments by applicants were made with respect to the Lym-1 and Lym-2 antibodies of Meyer, and noted that these antibodies are not B-cell antibodies, but are in fact HLA-DR antibodies that bind only at low levels normal B cells, and also that the Lym-1 and Lym-2 antibodies preferentially bind HLA class II in malignant B cells compared to normal B cells and monocytes, These statements in no way suggest that a skilled artisan would have any difficulty in implementing the present invention. A skilled artisan would not understand the Lym-1 or Lym-2 antibodies to be B-cell antibodies and would not select them for use in the present invention.

Turning now to the art-based rejections, the present claim amendments clearly obviate all of the art-based rejections that are pending, inasmuch as none of the cited art teaches or suggest a method of ablating or removing normal cells, and more particularly normal spleen cells, with a B-cell

[4] Action dated 4/23/2008, at page 15.

antibody. In this regard, it is noted that Meyer, cited in a rejection under Section 102 and as the primary reference in two rejections under Section 103, would not have suggested a method as presently claimed. Meyer relates to use of an anti-B cell antibody for suppressing the immune response generated upon administration of a therapeutic agent administered either as a naked or a conjugated antibody. Accordingly, there is no disclosure in Meyer that the anti-B-cell antibody is used to ablate normal cells, rather Meyer teaches how to combat the side effects arising from therapy using, for diagnostic or therapeutic purposes, an antibody (page 2, lines 38-42). The treatment modality may, according to Meyer also be used in connection with the use of therapeutic antibodies in the treatment of autoimmune diseases (page 3, lines 47-49). In other words, according to Meyer the side effects arising from the treatment of autoimmune diseases using antibodies may be treated using an antibody against the B-lymphocytes. Meyer does not teach method of ablating normal cells in a subject, comprising in which a therapeutically effective amount of a sterile injectable composition comprising a B-cell antibody or fragment thereof in a pharmaceutically acceptable injection vehicle is administered.

The examiner also repeats a rejection of claims under Section 102(b) based on Bussel *et al.* as evidenced by Grandamont *et al.* As noted in applicant's prior response, Grandamont *et al.* discusses the role of the Fc region of IVIG in treatment, as mentioned on page 3065 of that document, and fails to teach that IVIG includes B cell antibodies, let alone teaching or suggesting the use of B-cell antibodies in ablating normal cells in a subject. The primary mechanism of IVIG has been proposed to be the blockade of Fc-receptors, as reported in Teeling *et al.*, "Therapeutic efficacy of intravenous immunoglobulin preparations depends on the immunoglobulin G dimers: studies in experimental immune thrombocytopenia," *Blood*, 2001, Aug 15;98(4):1095-9, and applicant's previous comments are incorporated here by reference. Certainly the fact that Fc-fragments have the same activity in patients as IVIG goes against an assertion of any possible antibody effect of the preparation.

Even assuming, *arguendo*, that IVIG does include B-cell antibodies, it is clear that the amount is not sufficient to anticipate a claim which recites "a therapeutically effective amount" of B-cell antibody. The art clearly shows that the therapeutically active ingredient in IVIG is dimers interacting with Fcγ receptors, not B-cell antibodies. Accordingly, the rejection under Section 102(b) based on Bussel *et al.* as evidenced by Grandamont *et al.* is *prima facie* defective and reconsideration and withdrawal is respectfully requested.

Reconsideration and withdrawal of all art-based rejections is therefore respectfully requested.

In view of the foregoing, it is believed none of the references, taken singly or in combination, discloses the claimed invention, and therefore a notice of allowance is respectfully requested. If there are any problems with this response, applicant requests a further interview with the examiner, her supervisor and Ms. Brumbeck.

Respectfully submitted,

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